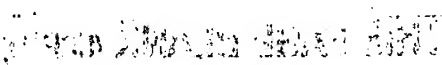
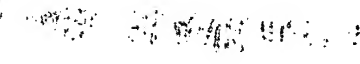


This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT 
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES 
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

THIS PAGE BLANK (USPTO)

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



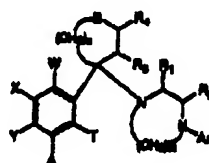
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 295/02, A61K 31/495, C07D 295/08, 239/42, 213/74, 317/58, A61K 31/505		A2	(11) International Publication Number: WO 96/14307 (43) International Publication Date: 17 May 1996 (17.05.96)
(21) International Application Number: PCT/US95/14472 (22) International Filing Date: 7 November 1995 (07.11.95) (30) Priority Data: 08/335,475 7 November 1994 (07.11.94) US 08/474,383 7 June 1995 (07.06.95) US 08/484,974 7 June 1995 (07.06.95) US (60) Parent Applications or Grants (63) Related by Continuation US 08/335,475 (CIP) Filed on 7 November 1994 (07.11.94) US 08/474,383 (CIP) Filed on 7 June 1995 (07.06.95) US 08/484,974 (CIP) Filed on 7 June 1995 (07.06.95) (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): PETERSON, John, M. [US/US]; 193 Lawrence Street, New Haven, CT 06511		(US). BLUM, Charles, A. [US/US]; 100 Mirror Lane, Guilford, CT 06437 (US). CAI, Guolin [US/US]; 38 Gray Ledge Drive, Guilford, CT 06439 (US). HUTCHISON, Alan [US/US]; 175 Bartlett Drive, Madison, CT 06443 (US). (74) Agents: SARUSSI, Steven, J. et al.; Banner & Allegretti, Ltd., Ten South Wacker Drive, Chicago, IL 60606 (US). (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published Without international search report and to be republished upon receipt of that report.	

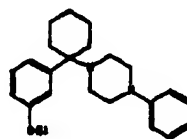
(54) Title: CERTAIN SUBSTITUTED BENZYLAMINE DERIVATIVES; A NEW CLASS OF NEUROPEPTIDE Y1 SPECIFIC LIGANDS

(57) Abstract

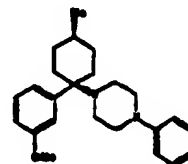
This invention encompasses compounds of formula (I) and the pharmaceutically acceptable salts thereof, wherein W, X, Y, A, and T represent organic or inorganic substituents, n is 1, 2, or 3, m is 2, 3, or 4, R₁-R₄ are hydrogen or organic substituents, and B is nitrogen, carbon, sulfur or oxygen, useful in the diagnosis and treatment of feeding disorders such as obesity and bulimia and cardiovascular diseases such as essential hypertension and congestive heart failure due to the binding of these compounds to human Neuropeptide Y1 receptors.



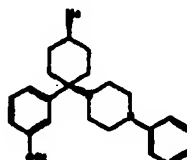
(I)



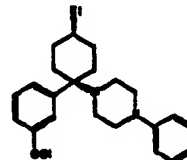
Compound 9



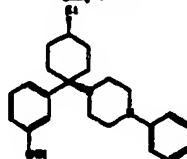
Compound 10



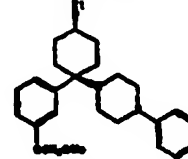
Compound 11



Compound 12



Compound 13



Compound 14

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

**Certain Substituted Benzylamine Derivatives;
A New Class of Neuropeptide Y1 Specific Ligands**

BACKGROUND OF THE INVENTION

5 Field of the Invention

This invention relates to certain substituted benzylamine derivatives which selectively bind to human Neuropeptide Y1 (NPY1) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds and compositions in treating feeding disorders and certain cardiovascular diseases.

10

Description of the Related Art

Neuropeptide Y, a peptide first isolated in 1982, is widely distributed in the central and peripheral neurons and is responsible for a multitude of biological effects in the brain and the periphery. Various animal studies have shown that activation of Neuropeptide Y1 receptors is related to vasoconstriction, Wahlestedt et al., Regul. Peptides, 13: 307-318 (1986), McCauley and Westfall, J. Pharmacol. Exp. Ther. 261: 863-868 (1992), and Grundemar et al., Br. J. Pharmacol. 105: 45-50 (1992); and to stimulation of consummatory behavior, Flood and Morley, Peptides, 10: 963-966 (1989), Leibowitz and Alexander, Peptides, 12: 1251-1260 (1991), and Stanley et al., Peptides, 13: 581-587 (1992).

20

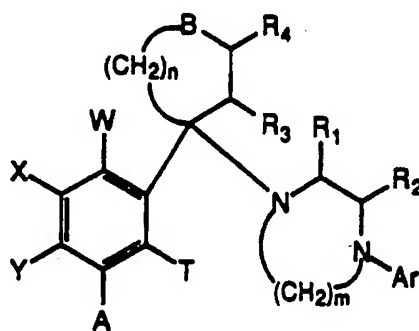
Grundemar and Hakanson, TIPS, May 1994 [Vol. 15], 153-159, state that, in animals, Neuropeptide Y is a powerful stimuli of food intake, and an inducer of vasoconstriction leading to hypertension. They further point out that low levels of Neuropeptide Y is associated with loss of appetite. These reports clearly indicate that compounds that inhibit the activity of this protein will reduce hypertension and appetite in animals.

SUMMARY OF THE INVENTION

Compounds that interact with NPY1 receptors and inhibit the activity of Neuropeptide Y at those receptors are useful in treating eating disorders such as, for example, obesity and bulimia, and certain cardiovascular diseases, such as, for example, hypertension.

- 5 This invention provides novel compounds of Formula I which selectively bind to Neuropeptide Y₁ (NPY₁) receptors. Such compounds are useful in treating feeding disorders such as obesity and bulimia as well as certain cardiovascular diseases such as essential hypertension.

- The invention also provides pharmaceutical compositions comprising compounds of
10 Formula I. The invention thus further relates to the use of such compounds and compositions in the treatment of eating as well as certain cardiovascular diseases. Accordingly, a broad embodiment of the invention is directed to a compound of Formula I:



I

where

Ar is an aryl group

B is sulfur, oxygen, a substituted nitrogen atom, or a mono- or disubstituted carbon atom;

n is 1, 2, or 3;

- 20 m is 2, 3, or 4;

W, X, Y, and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R₁ and R₂ independently represent hydrogen, or straight or branched chain lower alkyl having 1-6
5 carbon atoms; and

R₃ and R₄ are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms.

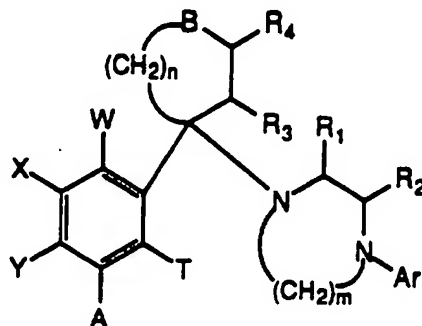
10 These compounds are highly selective partial agonists or antagonists at human NPY₁ receptors and are useful in the diagnosis and treatment of feeding disorders such as obesity and bulimia as well as certain cardiovascular diseases such as essential hypertension and congestive heart failure.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows representative substituted benzylamines of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I:



I

where

Ar is an aryl group preferably selected from the group consisting of phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

B is sulfur, oxygen, $N(R_5)$ or $C(R_5)(R_6)$;

n is 1, 2, or 3;

m is 2, 3, or 4;

W, X, Y, and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R_1 and R_2 are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R_3 and R_4 are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R₅ represents straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, or phenyl, 2-, 3-, or 4-pyridyl straight or branched chain lower alkyl having 1-6 carbon atoms; and

A and R₆ are the same or different and represent

5 hydrogen, hydroxyl, amino, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, or

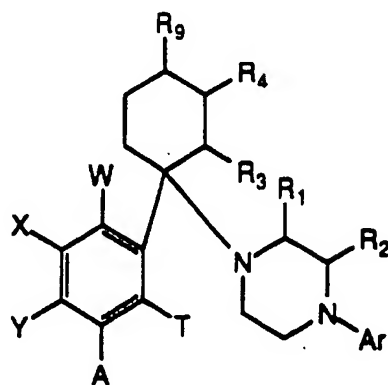
-(CH₂)_p-A'-(CH₂)_q-B' where

p is 0-5, q is 1-5, and A' is a direct bond, oxygen or sulfur, and

10 B' is hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, carboxyl, carboalkoxy, carboxamido, mono or dialkylcarboxamido, amino, or mono or dialkylamino.

15 Preferred compounds according to Formula I are those where Ar is optionally substituted phenyl, pyrimidinyl or pyridyl, B is carbon optionally substituted with phenyl or alkyl, and W, X, Y, A, T, and R₁-R₄ are hydrogen. Particularly, preferred compounds of Formula I are those where Ar is phenyl, pyrimidinyl or pyridyl, B is carbon optionally substituted with phenyl or alkyl, and W, X, Y, A, T, and R₁-R₄ are hydrogen.

20 The invention also relates to compounds of formula IA:

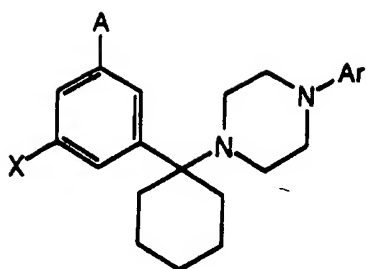


IA

where

- Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;
- A, W, X, Y, and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;
- R₁ and R₂ are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;
- R₃ and R₄ are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; and
- R₉ represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl.

The invention further encompasses compounds of Formula II:

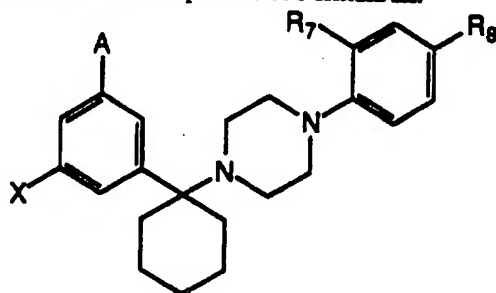


II

where A and X independently represent alkoxy and Ar represents phenyl, pyrimidinyl, or pyridyl.

Preferred compounds of Formula II are those where X and A are methoxy, ethoxy,
 5 isopropoxy, or butoxy, and Ar represents phenyl, pyrimidinyl, or pyridyl.

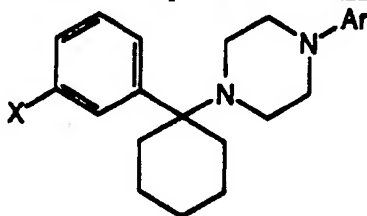
The invention further includes compounds of Formula III:



III

where X and A independently represent alkoxy and R7 and R8 are different and represent
 10 hydrogen or fluorine.

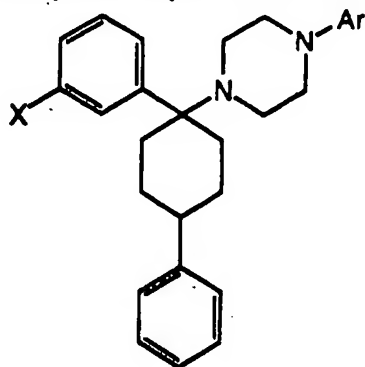
The invention further encompasses compounds of Formula IV:



IV

where X represents hydroxy and Ar represents phenyl, pyrimidinyl, or pyridyl.

The invention further encompasses compounds of Formula V:

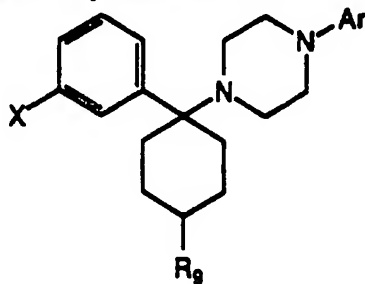


V

where X represents alkoxy and Ar represents phenyl, pyrimidinyl, or pyridyl.

- 5 Preferred compounds of Formula V are those where X is methoxy, ethoxy, isopropoxy, or butoxy, and Ar represents phenyl. Particularly preferred compounds of Formula V are those where X is methoxymethoxy or ethoxymethoxy.

The invention also includes compounds of Formula VI:

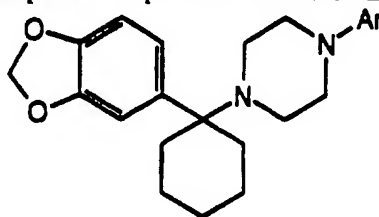


VI

10 where X represents alkoxy, R₉ is alkyl, and Ar represents phenyl, pyrimidinyl, or pyridyl.

- Preferred compounds of Formula VI are those where X is methoxy, ethoxy, isopropoxy, or butoxy, R₉ is alkyl, and Ar represents phenyl. Particularly preferred compounds of Formula VI are those where X is methoxy, ethoxy, isopropoxy, or butoxy, R₉ is methyl, and Ar represents phenyl. Other particularly preferred compounds of Formula VI are those where X is methoxymethoxy or ethoxymethoxy, R₉ is methyl, and Ar represents phenyl.
- 15

The invention also encompasses compounds of Formula VII:



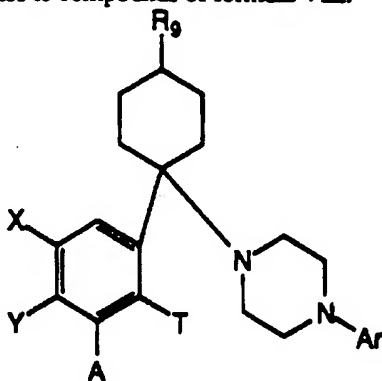
VII

5 where Ar represents optionally substituted phenyl, pyrimidinyl, or pyridyl.

Preferred compounds of Formula Ar represents phenyl, pyrimidinyl, or pyridyl.

Representative compounds of the present invention, which are encompassed by Formula I-VII, include, but are not limited to the compounds in Figure I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric,
 10 phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluene sulfonic, hydroiodic, acetic and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The invention also relates to compounds of formula VIII:



VIII

15

where

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

5 A, X, Y, and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; and

R₉ represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenyl.

10 The present invention also encompasses the acylated prodrugs of the compounds of Formula I-VIII. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

The invention encompasses both diastereomers of the compounds having 1,4-substitution on the cyclohexane ring. I.e., the invention encompasses both cis-, and trans-1,4-cyclohexanes. Preferred compounds of the invention having 1,4-substitution on the cyclohexane ring are those where the nitrogen atom forming the piperazine ring and the alkyl or phenyl group in the 4-position of the cyclohexane ring are "cis" with respect to each other. Thus, preferred compounds of the invention having such substitution are those that are cis-1-piperazinyl-4-alkyl or phenyl-
20 cyclohexanes.

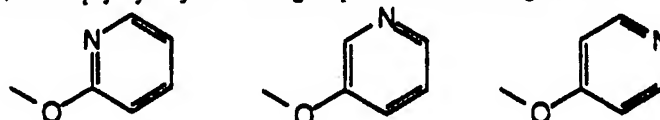
By "aryl" and "Ar" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which can optionally be unsubstituted or substituted with e.g., halogen, lower alkyl, lower alkoxy, lower
25 alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

By "alkyl" and "lower alkyl" is meant straight and branched chain alkyl groups having from 1-6 carbon atoms.

By "lower alkoxy" and "alkoxy" is meant straight and branched chain alkoxy groups having from 1-6 carbon atoms.

5 By "halogen" is meant fluorine, chlorine, bromine and iodine.

By 2-, 3-, and 4-pyridyloxy is meant groups of the following formulas respectively:



The pharmaceutical utility of compounds of this invention is indicated by the following assay for human NPY1 receptor activity.

10

Assay for Human NPY1 receptor binding activity

The procedure used is similar to that described by Gordon et al. (J. Neurochem. 55:506-513, 1990). SK-N-MC cells were purchased from ATCC (Rockville, MD). Cells were maintained at 37°C and 5% CO₂ in Dulbecco's modified essential media (DMEM) with L-glutamine and 110 mg/L sodium pyruvate, which was supplemented with 10% fetal bovine serum and 25 mM HEPES (pH 7.3). The binding assay was performed in 24-well plates (Falcon) when the cells were confluent. Taking care to not disturb the cells on the bottom of the wells, the media was aspirated, and 0.5 ml of Dulbecco's phosphate buffered saline (DPBS) with calcium and magnesium were added to each well. The DPBS was aspirated and an additional aliquot of DPBS was added and aspirated. To begin the assay, binding buffer consisting of serum-free DMEM containing 0.5% bovine serum albumin, 0.1% bacitracin and 0.1 mM phenylmethylsulfonylfluoride was added to each well. The cells and the binding buffer preincubated for 30 minutes at room temperature, at which point the drug dilution and [¹²⁵I]PYY (NEN-DuPont: 50000 -75000 cpm ~ 50 pM) were added to yield a final volume of 250 ul.

25 Nonspecific binding was defined with 1 mM NPY (porcine or human, Bachem California). After

a 3 hour incubation at room temperature, the plates were then put on ice and the wells were aspirated. The cells were washed 4-6 times with 0.5 ml of ice-cold DPBS. A dilute solution of Triton X-100 (1%) was then added to each well. After approximately 1 hour at room temperature, an aliquot from each well was transferred to a 12x75 mm testtube, and the amount of [125 I] was quantitated on a gamma counter with an efficiency of 80-85% (Genesys 5000, Laboratory Technologies). IC₅₀ values were calculated with the non-linear curve fitting program RS/1 (BBN Software Products Corp., Cambridge, MA). The binding characteristics for compounds of this invention are shown in Table 1.

TABLE I

<u>Compound Number</u> ¹	<u>IC₅₀(μM)</u>
9	0.137
13 (cis isomer)	0.067
18 (cis isomer)	0.075
20 (cis isomer)	0.076
21 (trans isomer)	0.525
29 (cis isomer)	0.039

10 1 Compound numbers relate to compounds shown in Figure I.

Compounds 13, 18, 20 and 29 are particularly preferred embodiments of the present invention because of their potency in binding to human NPY₁ receptors.

15 The compounds of general formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of
20 general formula I and a pharmaceutically acceptable carrier. One or more compounds of general

formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible
5 powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable
10 preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for
15 example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active
20 ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example
25 sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a

naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol
5 such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

10 Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the
15 addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for
20 example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for
25 example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters

with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a
5 preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a
10 solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

15 The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

20 Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

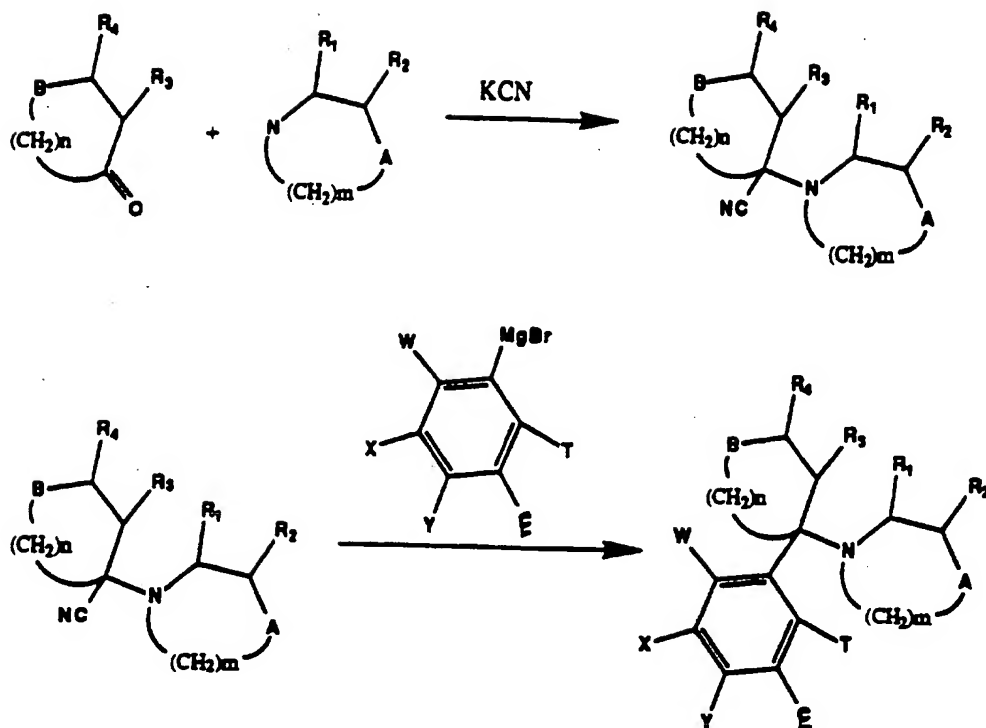
Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body
25 weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier

materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will
5 depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

An illustration of the preparation of compounds of the present invention is given in Scheme
I. Those having skill in the art will recognize that the starting materials may be varied and
10 additional steps employed to produce compounds encompassed by the present invention.

Scheme I



where

- 5 A is ArN or ArCH where Ar is phenyl, 2, 3, or 4 pyridyl, 2 or 3 thienyl, 2, 4 or 5 pyrimidyl either unsubstituted or mono or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;
- B is sulfur, oxygen NR₅ or CR₅R₆
- n is 1, 2, or 3;
- 10 m is 2, 3, or 4;
- W, X, Y, Z, T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

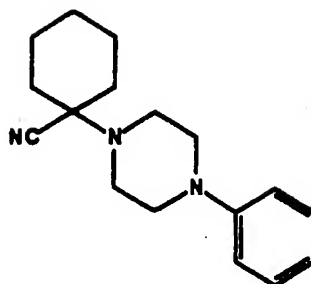
R₁ and R₂ are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R₃ and R₄ are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R₅ represents straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl, 2, 3, or 4 pyridyl, or phenyl, 2, 3, or 4 pyridyl straight or branched chain lower alkyl having 1-6 carbon atoms;

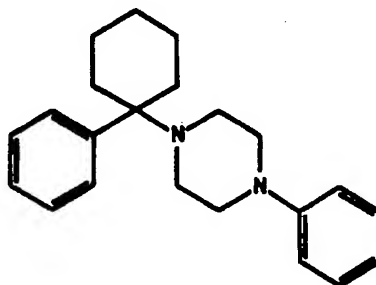
E and R₆ are the same or different and represent hydrogen, hydroxyl, amino, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2, 3, or 4 pyridyl, phenyloxy, 2, 3, or 4 pyridyloxy, or $-(CH_2)_p-A'-(CH_2)_q-B'$ where p represents 0-5 and q represents 1-5 and A' is a direct bond, oxygen or sulfur and B' is hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2, 3, or 4 pyridyl, phenyloxy, 2, 3, or 4 pyridyloxy, carboxyl, carboalkoxy, unsubstituted, mono or dialkylcarboxamido, amino, or mono or dialkylamino.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Example I

1-Phenylpiperazine (11.3 mL, 12 g, 75 mmol) was suspended in 100 mL water. The pH
5 was adjusted to 3 using 10% HCl. Cyclohexanone (7.8 mL, 7.4 g, 75 mmol) was added followed
by KCN (5 g, 75 mmol). The mixture was stirred 15 hours at room temperature during which
time the product solidified. The product was collected by filtration, washed with water, then
recrystallized from ethanol to give 14.5 g of 1-Cyano-1-(4-phenylpiperazin-1-yl)-cyclohexane as a
white solid (73 % yield), mp = 133-135 °C.

10

Example II

1-Cyano-1-(4-phenylpiperazin-1-yl)-cyclohexane (300 mg, 1.1 mmol) was dissolved in
15 10 mL ether under N₂ at room temperature. Phenyl magnesium bromide (4 mL of a 3 M ether
solution) was added and the reaction mixture stirred 15 hours. The mixture was diluted with 10
mL ether, transferred to a separatory funnel, washed 1 X 10 mL saturated NH₄Cl solution, then
extracted 3 X 10 mL 5 % HCl solution. The acidic extracts were basified using concentrated

NH₄OH solution then extracted 3 X 15 mL ether. The organic extracts were filtered through a silica gel pad then concentrated to afford 280 mg of the free base of the desired compound as a white solid (80 % yield). This material was dissolved in 5 mL ethyl acetate. Ethyl acetate saturated with HCl (5 mL) was added. 1-Phenyl-1-(4-phenyl-piperazin-1-yl)-cyclohexane dihydrochloride (Compound 1) which precipitated out of solution (88 mg) was collected by filtration, washed with ethyl acetate and dried *in vacuo*.

Example III

The following compounds were prepared essentially according to the procedure described in Examples I-II:

- a) 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride (Compound 2).
- b) 1-(3-Methoxyphenyl)-1-[4-(2-pyrimidinyl)-piperazin-1-yl]-cyclohexane dihydrochloride (Compound 3).
- c) 1-(3-Methoxyphenyl)-1-[4-(2-pyridinyl)-piperazin-1-yl]-cyclohexane dihydrochloride (Compound 4).
- d) 1-(3-Methoxyphenyl)-1-[4-(2-fluorophenyl)-piperazin-1-yl]-cyclohexane dihydrochloride (Compound 5).
- e) 1-(3-Methoxyphenyl)-1-[4-(4-fluorophenyl)-piperazin-1-yl]-cyclohexane dihydrochloride (Compound 6).

- f) 1-(3-Hydroxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
(Compound 7).
- g) 1-(3, 5-Dimethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
5 (Compound 8).
- h) 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
(Compound 9).
- 10 i) 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-phenyl-cyclohexane
dihydrochloride (cis isomer: Compound 10, trans isomer: Compound 11).
- j) 1-(3-*n*-Butoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
(Compound 12).
- 15 k) 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane
dihydrochloride (cis isomer: Compound 13, trans isomer: Compound 14).
- l) 1-(4-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
20 (Compound 15).
- m) 1-(2-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
(Compound 16).
- 25 n) 1-(3,4-Methenedioxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane
dihydrochloride (Compound 17).

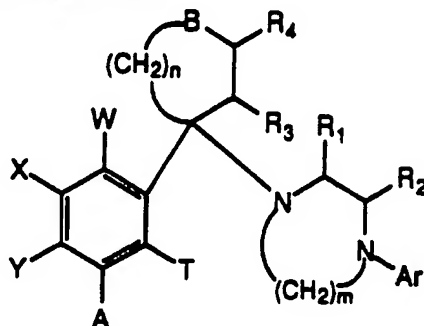
- o) 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane dihydrochloride (cis isomer: Compound 18, trans isomer: Compound 19).
- 5 p) 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-ethyl-cyclohexane dihydrochloride (cis isomer: Compound 20, trans isomer: Compound 21).
- q) 1-(3-Isopropoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane dihydrochloride (cis isomer: Compound 22, trans isomer: Compound 23).
- 10 r) 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-3-methyl- cyclohexane dihydrochloride (cis isomer: Compound 24, trans isomer: Compound 25).
- s) 1-(3-Benzoyloxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride
15 (Compound 26).
- t) 4-(3-Ethoxyphenyl)-4-(4-phenylpiperazin-1-yl)-tetrahydropyran dihydrochloride (Compound 27).
- 20 u) 4-(3-Ethoxyphenyl)-4-(4-phenylpiperazin-1-yl)-tetrahydrothiopyran dihydrochloride (Compound 28).
- v) 1-(3-Methoxymethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane dihydrochloride (cis isomer: Compound 29, trans isomer: Compound 30).
- 25

- w) 1-(3-Ethoxymethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane
dihydrochloride (cis isomer: Compound 31, trans isomer: Compound 32).
- x) 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methoxy-cyclohexane
5 dihydrochloride (cis isomer: Compound 33, trans isomer: Compound 34).

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred
10 embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

WHAT IS CLAIMED IS:

1. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein:

- 5 Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;
- B is sulfur, oxygen, N(R_5), or C(R_5)(R_6);
- n is 1, 2, or 3;
- 10 m is 2, 3, or 4;
- W, X, Y, and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;
- R_1 and R_2 are the same or different and represent hydrogen, or straight or branched chain lower
- 15 alkyl having 1-6 carbon atoms;
- R_3 and R_4 are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;
- R_5 represents straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl, 2-, 3-, or
- 20 4-pyridyl, or phenyl, 2-, 3-, or 4-pyridyl straight or branched chain lower alkyl having 1-6 carbon atoms; and

A and R₆ are the same or different and represent

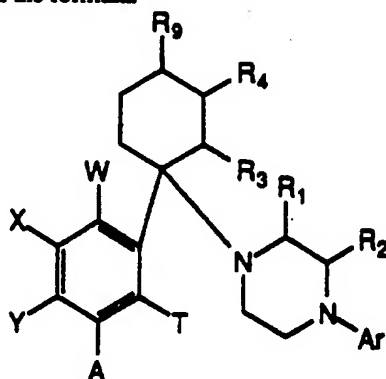
hydrogen, hydroxyl, amino, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, or

5 $-(CH_2)_p-A'-(CH_2)_q-B'$ where

p is 0-5, q is 1-5, and A' is a direct bond, oxygen or sulfur, and

B' is hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, carboxyl, carboalkoxy, carboxamido, mono or dialkylcarboxamido, amino, or mono or dialkylamino.

2. A compound of the formula:



15 where

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

A, W, X, Y, and T are the same or different and represent hydrogen, halogen, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

5 R₁ and R₂ are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

R₃ and R₄ are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; and

10 R₉ represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenyl.

3. A compound according to Claim 2 wherein A is lower alkoxy.

15 4. A compound according to Claim 1 which is 1-Phenyl-1-(4-phenylpiperazin-1-yl)-cyclohexane.

5. A compound according to Claim 1 which is 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.

20 6. A compound according to Claim 1 which is 1-(3-Methoxyphenyl)-1-[4-(2-pyrimidinyl)-piperazin-1-yl]-cyclohexane.

25 7. A compound according to Claim 1 which is 1-(3-Methoxyphenyl)-1-[4-(2-pyridinyl)-piperazin-1-yl]-cyclohexane.

8. A compound according to Claim 1 which is 1-(3-Methoxyphenyl)-1-[4-(2-fluorophenyl)-piperazin-1-yl]-cyclohexane.
9. A compound according to Claim 1 which is 1-(3-Methoxyphenyl)-1-[4-(4-fluorophenyl)-piperazin-1-yl]-cyclohexane.
10. A compound according to Claim 1 which is 1-(3-Hydroxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.
- 10 11. A compound according to Claim 1 which is 1-(3, 5-Dimethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.
12. A compound according to Claim 1 which is 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.
- 15 13. A compound according to Claim 1 which is both diastereomers of 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-phenyl-cyclohexane.
14. A compound according to Claim 1 which is 1-(3-*n*-Butoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.
- 20 15. A compound according to Claim 1 which is both diastereomers of 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane.
- 25 16. A compound according to Claim 1 which is 1-(4-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.

17. A compound according to Claim 1 which is 1-(2-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.

5 18. A compound according to Claim 1 which is 1-(3,4-Methenedioxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane.

19. A compound according to Claim 1 which is both diastereomers of 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane.

10

20. A compound according to Claim 1 which is both diastereomers of 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-ethyl-cyclohexane.

21. A compound according to Claim 1 which is both diastereomers of 1-(3-Isopropoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane.

15

22. A compound according to Claim 1 which is both diastereomers of 1-(3-Methoxyphenyl)-1-(4-phenylpiperazin-1-yl)-3-methyl-cyclohexane.

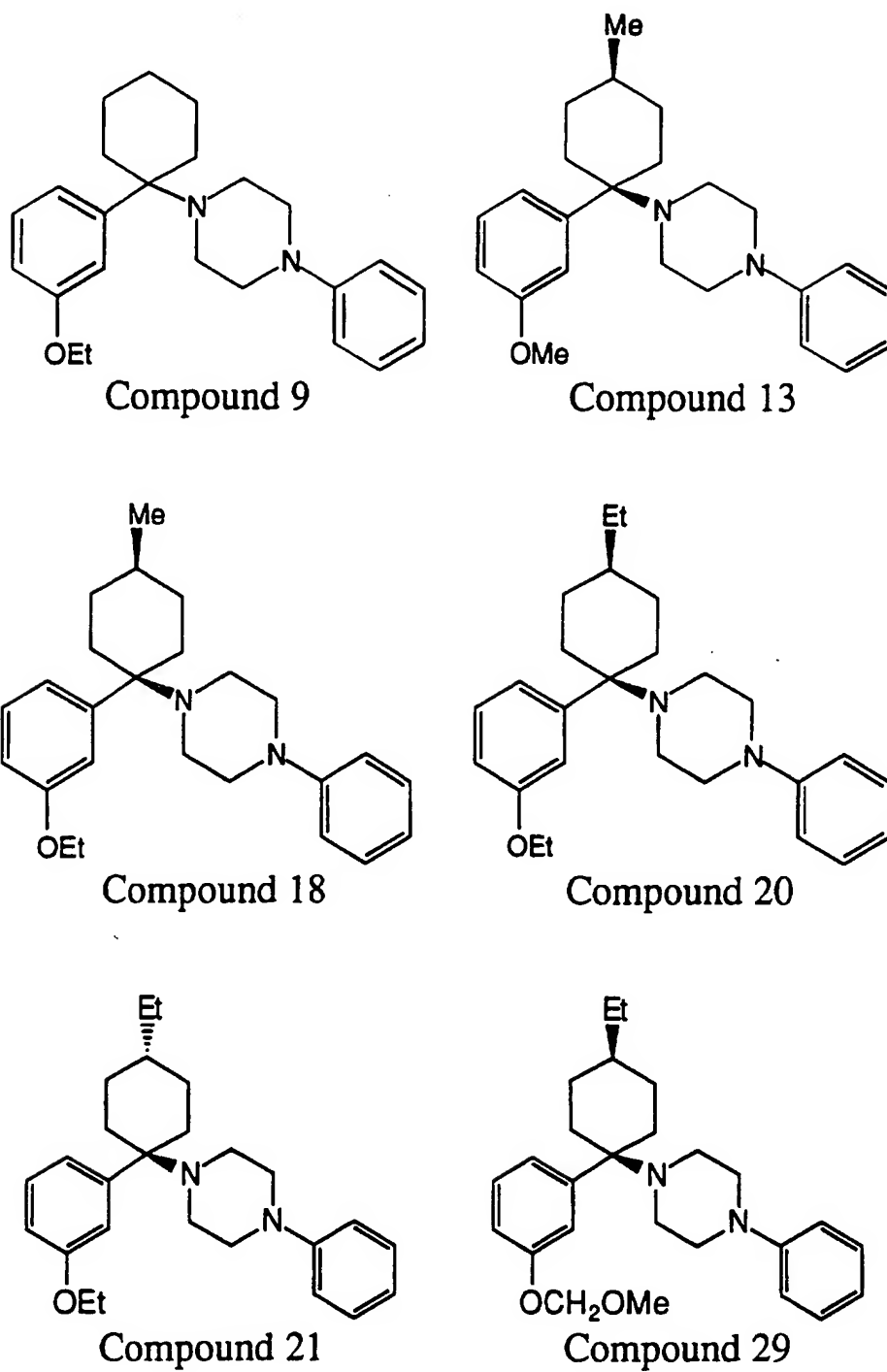
20 23. A compound according to Claim 1 which is 1-(3-Benzoyloxyphenyl)-1-(4-phenylpiperazin-1-yl)-cyclohexane dihydrochloride.

24. A compound according to Claim 1 which is 4-(3-Ethoxyphenyl)-4-(4-phenylpiperazin-1-yl)-tetrahydropyran.

25

25. A compound according to Claim 1 which is 4-(3-Ethoxyphenyl)-4-(4-phenylpiperazin-1-yl)-tetrahydrothiopyran.
26. A compound according to Claim 1 which is both diastereomers of 1-(3-Methoxymethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane.
27. A compound according to Claim 1 which is both diastereomers of 1-(3-Ethoxymethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methyl-cyclohexane.
28. A compound according to Claim 1 which is both diastereomers of 1-(3-Ethoxyphenyl)-1-(4-phenylpiperazin-1-yl)-4-methoxy-cyclohexane.

Figure 1



INTERNATIONAL SEARCH REPORT

In national Application No
PCT/US 95/14472

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/02 C07D295/08 C07D239/42 C07D213/74 C07D317/58
A61K31/495 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CHEMICAL ABSTRACTS, vol. 123, no. 7, 14 August 1995 Columbus, Ohio, US; abstract no. 83312, AL-DEEB, O., A. ET AL. 'Synthesis of new (1-phenylcyclohexyl)piperazine derivatives as potential analgesics' see abstract	1-4,17
X	& BULL. FAC. PHARM. (CAIRO UNIV.), vol. 31, no. 3, 1993 pages 475-479, AL-DEEB, O., A. ET AL. see the whole document	1-4,17
A	US,A,4 845 221 (STACK, G., P.; PODLESNY, E., J. ;) 4 July 1989 see the whole document	1-28
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

20 March 1996

Date of mailing of the international search report

26. 04. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Traegler-Goeldel, M

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 95/14472

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 395 312 (JOHN WYETH & BROTHER LIMITED) 31 October 1990 see the whole document ---	1-28
A	TIPS, vol. 15, May 1994 pages 153-159, GRUNDEMAR, L. AND HAKANSON, R. cited in the application -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/14472

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4845221	04-07-89	NONE	
EP-A-395312	31-10-90	AU-B- 619677	30-01-92
		AU-B- 5377890	25-10-90
		AU-B- 619678	30-01-92
		AU-B- 5377990	25-10-90
		EP-A- 0395313	31-10-90
		FI-B- 93832	28-02-95
		GB-A,B 2230780	31-10-90
		GB-A,B 2230781	31-10-90
		GB-A,B 2255976	25-11-92
		HK-A- 171395	17-11-95
		IL-A- 94151	31-08-95
		IL-A- 94160	24-06-94
		JP-A- 3011059	18-01-91
		JP-A- 3020263	29-01-91
		US-A- 5340812	23-08-94
		US-A- 5420278	30-05-95
		US-A- 4921958	01-05-90
		US-A- 4988814	29-01-91
		US-A- 5364849	15-11-94
		US-A- 5382583	17-01-95